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MSS. intended for publication and books, etc., intended for review should be sent to Professor J. McKeen Cattell, Garrison-on-Hudson, N. Y.

THE PHYSICO-CHEMICAL CONDITIONS OF ANESTHETIC ACTION[1]

UNDER certain well-defined artificial conditions, as well as under some that are normal, the living system—organism, tissue or cell—becomes temporarily inactive and irresponsive to stimuli. When such an artificially induced state of inhibition is well marked and lasting it is called anesthesia, or in a somewhat more restricted sense, narcosis. This condition may last for hours or even days, but apparently not indefinitely; and when it passes off the normal vital activities and properties return unimpaired. This apparently complete *reversibility* is one of the most remarkable features of anesthesia, and distinguishes it from death—a perhaps related but characteristically irreversible change. The terms "anesthesia" and "narcosis" are somewhat differently applied, although they have the same essential significance; the former relates to any temporarily insensitive condition, however produced, while "narcosis" usually means an anesthesia produced by chemical substances. I shall use the term anesthesia throughout the present address to designate any temporary or reversible lowering or loss of the normal vital responsiveness, or of the normal automatic vital activity, under the influence of certain artificial substances or conditions. Anesthesia, as thus defined, may be exhibited by the most various organisms and cells, if not by all. It is fully as characteristic of plant cells as of animal cells, although its manifestations may be less obvious and striking

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in the former group of organisms. In its most familiar aspect the complete organism, *e. g.*, a man, or an isolated living tissue, as a nerve or muscle, fails during anesthesia to show any response to a stimulus which normally excites it strongly. In other words, the capability of responding to stimuli—what we call "irritability"—is in anesthesia diminished or lost. When the condition passes off the normal responsiveness returns unimpaired. Thus a muscle exposed to ether vapor soon ceases to contract on stimulation; under the same conditions a nerve ceases to conduct; in motile plants like sensitive plants the characteristic osmotic motor mechanisms cease to act. Automatic activities like ameboid movement, ciliary movement, protoplasmic flowing, cell division, and growth may also be brought temporarily to a rest by anesthetics. Claude Bernard showed long ago that seedlings ceased growth in an ether-impregnated atmosphere, and resumed it when the ether was removed. Fertilized egg-cells cease to divide in the presence of an anesthetic in appropriate concentration, although they remain living and proceed with cell-division and development when the anesthetic is removed. Other less evident cell-processes, including metabolism, are similarly affected; the rate of oxidation is usually slowed during anesthesia, though there are exceptions to this rule.

It should be remembered that such decrease of the vital activity or responsiveness is not a solely artificial phenomenon. Conditions physiologically resembling anesthesia occur normally in the life of many organisms; sleep is in fact a kind of physiological regularly recurring narcosis due apparently to accumulation of certain metabolic products in the blood or tissues. Again, all irritable tissues lose their responsiveness for a brief period following excitation; this is the so-called "refractory period," which has been compared with narcosis by some physiologists. The resemblance in this case is probably superficial; but I call attention to this phenomenon in order to show once more that temporary loss of irritability may occur under normal or physiological conditions as well as under artificial. There are also noteworthy resemblances between narcosis and fatigue. Thus the degree of irritability of a tissue may vary within a wide range under normal as well as artificial conditions.

We shall first inquire under what general conditions irritable tissues undergo reversible decrease or loss of irritability. These conditions are various. One of them is cold. The living system operates within a narrow range of temperature. Most irritable tissues or cells become less responsive or lose irritability as the temperature approaches zero. In a muscle or nerve of a cold-blooded animal the ability to respond to stimulation is not necessarily decreased by a moderate reduction of temperature—in fact, slight cooling may increase the irritability of nerve; the tissue responds in the typical manner, but the *rate* of the response—as indicated by the duration of the single contraction in muscle or of the electrical variation in nerve—is always decreased, typically to a degree corresponding to the usual temperature-coefficient of chemical reaction-velocity. In the neighborhood of zero stronger stimuli becomes necessary to elicit a response, and eventually none may appear. Different organisms vary in these respects. In some animals, as tropical medusæ, irritability is abolished or greatly lowered at a temperature considerably above zero. The same is true of warm-blooded animals. On return to normal temperature irritability is restored.

Another condition producing effects resembling anesthesia is lack of oxygen. This

retards or arrests activity in many cases; *e. g.*, the nerve cells of vertebrates are very susceptible to lack of oxygen; nerve trunks, on the other hand, are relatively insusceptible. Cell-division—*e. g.*, in developing egg-cells—usually ceases if the oxygen supply is insufficient. Contractile activities are decreased or abolished. Many organisms, however, show only slight immediate effects; this is true of many Protozoa; Vorticellæ, for instance, remain contractile for some time after simple removal of oxygen from the medium, although they are at once paralyzed by anesthetics. Such facts oppose the view held by Verworn and others, that the anesthetic acts primarily on the oxidative mechanism of the cell. It is true that the rate of oxidations in active tissues is lowered during anesthesia, but this effect is rather a consequence than a cause of the lessened activity. Obviously wherever free oxygen is necessary to the normal activities of a tissue its withdrawal will arrest those activities. But the effects produced by lack of oxygen are not to be identified with anesthesia because of such incidental resemblances.

There are also a number of physical conditions that may deprive a cell temporarily of irritability. Thus mechanical shock may have this effect, which, however, is probably to be regarded as essentially a consequence of over-stimulation, causing abnormal prolongation of the refractory period.[2] The same is probably true of the insensibility produced by strong electrical currents. Under certain conditions, however, the electric current may produce effects closely resembling typical anesthesia. This occurs when a weak constant current is passed through an irritable tissue like muscle or nerve; during the flow of the current the irritability of the tissue is modified in the neighborhood of the two electrodes, being heightened at the cathode and lowered at the anode; and in this latter region the nerve may become completely insensitive to stimuli that ordinarily cause strong excitation. The inexcitable state thus produced is called "anelectrotonus"; it is in reality a form of local anesthesia, and as such has been employed for the alleviation of pain in sciatica and similar conditions. Muscle is affected in a similar manner; the frog's heart may thus be rendered locally incapable of contraction, as in the simple class-experiment familiar to all physiologists. This action of the current probably depends on its altering the electrical polarization normal to the membranes of the irritable elements—only in a direction the inverse of that causing stimulation.[3] There is much evidence that the state of polarization of the semipermeable membranes bounding the irritable elements is an important factor in determining the degree of responsiveness to stimulation; the facts of electrotonus indicate that by altering the polarization by an external current the irritability of the tissue may be changed in the direction either of increase or of decrease.

Irritability may, however, be more readily modified by the use of chemical substances than by any other means, and, as is well known, many such substances are in daily use in medical and surgical practise for procuring local or general insensibility to pain—hence the application of the name "anesthetic" to the large class of substances possessing this property. When we inquire into the chemical nature of such substances we find that anesthetic property is confined to no special class, but is ex-

[2] This apparently corresponds to the period of increased permeability and depolarization accompanying stimulation.

[3] *I. e.*, reinforcing instead of diminishing the normal or physiological polarization of the membranes.

hibited by substances of the most diverse chemical character. Acids in low concentration depress the irritability of many tissues; in some cases alkali has this effect; gases like carbon dioxide and nitrous oxide have marked anesthetic action; solutions of magnesium, calcium and strontium salts cause local anesthesia in frog's muscle and nerve; pure solutions of sugar and other indifferent non-electrolytes have similar effects; in these tissues irritability depends on the presence of certain electrolytes, especially sodium salts, in the media and returns on replacing the tissues in solutions containing these salts. But the most significant relationships are seen in the case of the large class of substances, differing widely in chemical constitution and properties, which possess in common the physical property of dissolving fats or of dissolving in fats. These substances include the majority of the anesthetics in common use, as ether, chloroform, ethyl chloride, urethane, etc. The connection between fat-dissolving power and anesthetic property was in fact early recognized—first by Bibra and Harless in 1847; and this relationship is of great physiological significance, since it indicates that the anesthetic is selective in its action on the cell constituents, and produces its effects by changing the state of fatty or fat-like substances in protoplasm. It indicates further that the state of these substances determines the degree of irritability of the cell. All cells, so far as known, contain such substances; they are the so-called "lipoids" which include lecithin and cholesterin, and various other ether-soluble compounds of usually complex constitution. Historically these substances were first grouped into a class simply on account of their fat-like solubilities, so that they form, chemically speaking, a somewhat heterogeneous group, some members of which, as cholesterin, are not fats in any sense. Others, as lecithin, are more closely related to the fats proper. They appear to be invariable constituents of protoplasm—a fact which in itself is not surprising in view of the amino-acid constitution of proteins: since proteins are largely derivatives or condensation-complexes of amino-fatty acids, fat-like substances might be expected to appear in cells during metabolism. It is clear, however, that these substances are not mere by-products of protein metabolism, or reserve material like fats, but play a fundamental rôle in cell-processes; the profound physiological effects produced by all lipoid-solvent substances are a sufficient proof of this, although regarding the precise nature of this rôle we know little as yet. In some intimate way the lipoids appear to be essential to the irritability of the cell, and altering their state causes corresponding changes of irritability.

About fifteen years ago Overton and Hans Meyer investigated the relation between the lipoid-solvent power of a large number of organic anesthetics and the intensity of their narcotic action, and reached independently the conclusion that the chief factor determining this action was the value of the partition-ratio of the anesthetic between water and a typical lipoid like lecithin. That is, for any series of lipoid-soluble compounds the narcotic action increases as the lipoid-solubility increases and the water-solubility decreases. These two solubilities usually show an inverse relation to each other. Now, the view that this form of anesthetic action depends essentially upon a modification of the cell-lipoids—which was put forward simultaneously and independently by Overton and Meyer—is undoubtedly well founded, and is accepted by most physiologists, even although in the absence of any definite and final knowledge of the physiological rôle

of these cell-constituents it is far from being a complete theory of anesthesia. Such a theory would evidently involve a complete theory of stimulation, and this can hardly be said to exist as yet. It is, however, possible, I believe, to gain further insight into the nature of anesthetic action by combining the results of these and similar experimental studies of anesthesia with the results of certain more recent studies of the nature and conditions of the process of normal stimulation. It is necessary to form some clear conception of the nature of the changes involved in stimulation before we can profitably consider the question of just how the stimulation-process is modified by the presence of the anesthetic.

Before considering in more detail the mechanism of stimulation and of its modification by anesthetics, let us first consider briefly the nature of the physico-chemical constitution of the living cell, as more recent research has led us to conceive of it. This is a subject which is not easy to summarize, and on which much light remains to be thrown. It is clear, however, that the living protoplasm is not a homogeneous solution, but is a "polyphasic system"; *i. e.*, a mixture consisting of various substances and solutions which are only partly miscible with one another, and are thus interrelated like the different phases of an emulsion or similar system. These several phases, which are partly solid, partly liquid, appear in each living cell to have a constant and definite arrangement, whose exact nature varies characteristically from cell to cell. There appears typically to be a solid or semi-solid structural substratum consisting of colloidal material, most of which is in a water-swollen or hydrated state; in addition to this more fixed and permanent part of the cell-organization, numerous simpler substances are present—sugars, salts, amino-acids and others—largely in a state of simple aqueous solution, but probably partly adsorbed at the surfaces of the colloidal phases. There is evidence that it is by the oxidation of certain of these substances, especially sugar, rather than of the colloidal material, that most of the energy manifested in the cell-processes is set free. The colloidal substratum furnishes the conditions under which the energy-yielding oxidations and other metabolic changes take place, and apparently determines their course, character and velocity. The solid colloidal material of the cell may in one sense be considered as by-product of the metabolic activities of the protoplasm; it appears, once formed, to undergo itself relatively slight change, but to influence profoundly, by its presence and arrangement, the character of cell-metabolism.[4] The colloids are of varied chemical nature; they are chiefly proteins and lipoids, and it is to be noted that they are built up by various forms of molecular union and polymerization from relatively simple substances furnished by the environment. This is true not only of plants, but also of the individual cells of higher animals, where the material which goes to form proteins reaches the cell in the form of amino-acids, or of simple polypeptides.[5] In general it is from such amino-acids together with salts and carbohydrates that the cell builds up the colloids which form its characteristic structural apparatus. This appears highly complex in some forms of irritable tissue, as in voluntary muscle; in others, as in nerve, the essential structure appears relatively simple. What we call the "structural organization" of the cell is merely another name for the physical char-

[4] *Cf.* Child's interesting discussion of the relation between metabolism and structure in the *Journal of Morphology*, Vol. 22, 1911, p. 173.

[5] *Cf.* Folin's recent papers in the *Journal of Biological Chemistry.*

acteristics and arrangement of the solid colloidal material.

However simply organized a cell may seem, there are certain elements of structure which appear always to be present, and to play a fundamentally important rôle in stimulation and in other life-processes. These are the *membranes*. Most, if not all, living cells are delimited from the medium in which they live by thin semi-permeable colloidal surface-films, the so-called plasma-membranes. Similar semi-permeable partitions are often found in the cell-interior, *e. g.*, about nuclei, vacuoles, chromatophores, and other structures. They appear to be formed of the same colloids as the other protoplasmic structures, namely, proteins and lipoids. These colloids, like many other organic substances, have, when dissolved in water, a marked influence in lowering the surface-tension of the solvent. Any substance thus acting tends, by the operation of Gibbs's principle, to collect or condense on the free surfaces; if the substance is colloidal in nature it may there pass out of solution and form a solid surface-film or membrane; and it is probably under conditions essentially like these that the cell-membranes are formed. Artificial membranes similar in many of their properties to the plasma or nuclear membranes of cells may be formed in protein solutions about droplets of chloroform, mercury or other water-immiscible substances. Now the plasma-membranes of irritable cells undoubtedly play a fundamentally important part in stimulation, as will be seen below, so that it will be necessary to consider first some of the essential properties of these membranes before passing to the consideration of the stimulation-process itself and its modification by anesthetics.

The plasma-membranes are typically *semi-permeable* structures—so much so that living cells form in many cases the most convenient and rapidly acting osmometers that we possess. If we place living cells, like plant-cells or blood corpuscles, in solutions of sugars, neutral salts and various other substances not in themselves immediately injurious to the cells, osmotic effects result from which the osmotic pressure of the solution relatively to that of the cell-contents can be estimated with great accuracy—as the researches of de Vries, Overton, Hedin and many others have shown. Two provisos are necessary in making use of living cells as osmometers: first, the dissolved substance must not by its own action impair the semi-permeability of the membrane, and second, it must not appreciably penetrate the membrane during the time occupied by the experiment. The plasma-membranes are in fact semi-permeable only in relation to certain classes of substances; towards others they show themselves freely permeable, and the character of these substances is important, because indication is thus afforded of the chemical nature of the materials composing the membranes. This is a matter of fundamental importance in the theory of anesthesia. Let us take for example a tissue composed of typical irritable cells, such as a frog's voluntary muscle. In studying the osmotic properties of this tissue, Overton found many years ago that the cells behaved in solutions of certain substances as if they were enclosed by strictly semi-permeable membranes; the chief of such substances are sugars, neutral salts, polyatomic alcohols like mannite, and amino-acids like glycocoll; but toward a large series of mainly organic substances, including alcohols, esters, aldehydes, hydrocarbon-derivatives and others, the membranes behaved as if freely permeable. Thus in an $m/8$ (0.7 per cent.) solution of NaCl the muscle retains its weight unaltered, neither absorbing nor losing water; similarly in solutions

of sugar, mannite or glycocoll of the same osmotic pressure (of about 6 atmospheres). But if to an $m/8$ NaCl solution we add (*e. g.*) alcohol in sufficient quantity to double the total osmotic pressure of the solution, it is found that there is no perceptible increase in its osmotic action on the muscle; in other words, the alcohol acts as if it entered the cell with the same readiness as the water. Many other substances show a similar power of freely entering the cell; others like urea, glycol and glycerine also enter, but more slowly. Similar observations in both animal and plant cells have shown that readiness of entrance into cells is a property that is closely correlated with solubility in fats or fat-like substances, including lipoids like lecithin. Substances not so soluble usually gain entrance slowly or imperceptibly. Overton drew from these facts the conclusion that the outer limiting layer or plasma-membrane of living cells consists in large part of lipoids, and that the characteristic osmotic properties of the cell depend on the presence of these substances in the membrane. Since substances that dissolve in lipoids will pass readily through lipoid-impregnated partitions, this view explains why plasma-membranes are in fact readily permeable to such substances as a class. In its detailed application Overton's view has met with considerable opposition; thus, according to Overton, intra-vitam dyes like neutral red and methylene blue enter cells readily *because of* their solubility in lipoids; a certain number of exceptions to this rule have been pointed out by Ruhland and others; but in spite of these discrepancies there seems no doubt—when the whole of the evidence is considered—of the truth of Overton's main contention that lipoid-solubility strongly furthers the ready entrance of substances into cells. Traube believes that the degree of surface-activity, rather than of simple lipoid-solubility, is the determining factor; this property shows a general parallelism with the lipoid-water partition-coefficient, and hence also with the readiness of penetration. But there appear to be more exceptions to Traube's rule than to Overton's, while there are other and independent indications that the surface-films of cells are characteristically rich in lipoids; for instance, the fact that in the eggs of sea-urchins and other animals lipoid-solvents are especially effective in causing the formation of fertilization membranes (a typical surface-effect) and in initiating cell-division; also the facts which I shall cite presently, showing that lipoid-solvents are characteristically effective in altering the permeability of the plasma-membranes and in modifying their resistance to alteration by cytolytic substances.

I dwell upon these researches here because of the light which they throw on the question of the constitution of the plasma-membranes of cells, including those of the irritable tissues. They indicate that the membranes—and perhaps surface-structures in general—are especially rich in lipoids. Now lipoid-soluble substances will tend, by the operation of the partition-law, to concentrate in the lipoids of the tissue; they will thus tend to gather in the membranes, and in so doing they will necessarily modify the physical state of these structures and so influence their physiological properties. We have already seen that the most striking effect which lipoid-solvents produce on irritable tissues is to modify their irritability, and under certain conditions to suppress it altogether. This suggests that the membranes have a special relation to stimulation. We should expect on *a priori* grounds that the excitatory apparatus of the cell should be externally situated; and we are thus led to inquire if there is other and independent evidence

that the surface-films or plasma-membranes of the irritable elements play any such special part in stimulation.

There are in fact many indications that this is the case. Investigation of the conditions of electrical excitation—undertaken quite without reference to the problem we are considering—has shown that the semi-permeable membranes of irritable tissues are intimately concerned in stimulation. The first definite proof of this was brought forward in 1899 by Nernst. He was struck with the fact that Tesla currents (or alternating currents of high frequency) may be passed through irritable tissues (or through the human body) without causing stimulation; while if the frequency of the current is sufficiently lowered, but without altering its intensity, strong stimulation results. Now what does this mean? Evidently that the current must flow for a certain minimal time in a *constant direction* in order to stimulate. Mere conduction of a given quantity of electricity through an irritable tissue is not in itself sufficient to cause stimulation. There is some kind of cumulative effect depending on a steady flow in one direction. What physical peculiarities of the living tissue condition this remarkable peculiarity? Nernst pointed out that a living tissue in its relation to the electric current is an electrolytic conductor, which, however, is not homogeneous like an ordinary salt-solution, but peculiar in being sub-divided at intervals by semi-permeable partitions, the cell-membranes. When therefore the current starts to flow it carries as usual anions toward the anode and cations toward the cathode, but at the semi-permeable membranes this movement is blocked; the concentration of anions thus tends to rise above that of cations on the side of the membrane facing the cathode and *vice versa,* and the above behavior of the tissue may be partly explained if we assume that these changes of concentration must reach a certain degree if stimulation is to result. For this effect time is required. Hence, if the current is reversed too soon, the stimulating effect is annulled, and the tissue remains unaffected. Now, if the assumption is true that stimulation is the expression of a change of electrical polarization, due to a change in the concentration of ions at the membranes, the time during which the current must flow in order to produce a given polarization-effect ought to correspond with that needed for a given stimulation-effect. Nernst's analysis shows that the polarizing action varies directly with the intensity of the current (*i. e.,* the quantity of electricity—*i. e,* ions —transported in unit time) and with the square root of its duration ($S = Ki\sqrt{t}$), and observations on a variety of irritable tissues have shown that the stimulating action of a given current does vary in essentially this manner with the duration of its flow in one direction (*i. e.,* inversely with the square root of the number of alternations in the case of an alternating current). It seems clear then that electrical stimulation is dependent on the polarization-changes produced by the current at the semi-permeable membranes of the irritable elements.

One main result of these investigations is thus to localize the stimulating action of the current at the semi-permeable membranes, and to indicate that a change in the electrical polarization of these membranes is an essential feature of stimulation. It is evident that this result does not constitute a complete analysis of the nature of stimulation. But it indicates that some change in the membrane is essential to this process. An electrical variation accompanies every normal stimulation and undoubtedly forms an inseparable feature of the process, but its conditions are still imperfectly under-

stood. There is evidence, however, that it is associated with a definite alteration in the osmotic properties of the membrane. The electrical properties of irritable tissues like muscle indicate that during life there exists permanently in the resting cell a difference of potential, equal roughly to 1/10 volt, between the outer and inner surfaces of the plasma-membrane. When the uninjured outer surface of a muscle or nerve is connected through a galvanometer with the exposed interior of the elements (cut surface) a current, the so-called "demarcation-current," flows from exterior to interior, indicating that the outer surface of the cells or nerve fibers has a higher potential than the interior. This potential-difference appears dependent on the semi-permeability of the plasma-membrane; it is absent in dead cells whose plasma-membranes have lost their semi-permeability, and it is diminished by the application of poisons which impair the normal semi-permeability. Briefly, the demarcation-current potential appears in some way to be inseparably connected with this semi-permeability of the membrane. Ostwald in 1890 suggested a possible explanation of this condition when he pointed out that a membrane might become the seat of a potential difference by interfering unequally with the diffusion of the anions and cations of an electrolyte contained within the cell. If the plasma-membrane allowed cations to pass outward freely, but prevented the passage of anions, a state of things would be produced comparable to what we observe in living cells. But the actual conditions are probably more complex than this, and experimental substantiation of Ostwald's suggestion has not been satisfactory. The subject is evidently one requiring further investigation. In any case, however, the existence of the demarcation-current potential appears dependent on the semi-permeability of the membrane, and whenever the latter undergoes marked increase of permeability, this potential is invariably decreased. The electrical variation or action-current which normally accompanies stimulation may be theoretically accounted for by assuming that at this time the membrane undergoes a decided but temporary increase in permeability, *i. e.*, loses the semi-permeable properties which it possesses during rest, and there is independent evidence that this change actually occurs during stimulation. If this is the case the plasma membrane is the seat of the most constant and characteristic manifestation of stimulation—the electrical variation or action-current. The membrane responds to the stimulating condition by suddenly changing its permeability and hence its electrical polarization.

We are thus brought to the conclusion that the plasma-membrane is characteristically and intimately concerned in the stimulation process. During stimulation it appears to undergo a sudden and quickly reversible increase of permeability. The electrical variation is one expression of this change, but there are others as well. Thus the movements of sensitive plants, which occur under the same conditions of stimulation as those of irritable animal tissues, are due to a collapse of turgid cells, consequent upon a sudden loss of the semi-permeable properties of the plasma-membranes enclosing the osmotically active solution or cell-sap. Here at least is one irritable tissue where the connection between permeability-increase and stimulation seems unmistakable. It might be held that the existence of special osmotic motor mechanisms in certain plants affords no indication of the nature of the conditions in irritable animal cells; but even in animals there are in some cases very clear indications that stimulation is constantly associated with an increase

of permeability, as I shall shortly point out. Evidence from various sides thus proves the participation of the plasma-membranes in the stimulation-process. Just why a change in the permeability and electrical polarization of the plasma-membrane should influence so profoundly the metabolic and other activities of the cell is naturally a far-reaching question requiring further investigation, but there are many reasons for believing that the primary or initiatory phase of the stimulation-process is a change of this nature.

Let us return now to the question of why anesthetics interfere with the stimulation-process. In the first place they can be shown experimentally to interfere with both of the above characteristic manifestations of stimulation, (1) the action-current and (2) the change of permeability. If these are the critical or primary events, on which the other effects following stimulation depend, it is evident that suppression of these must involve a suppression of the entire series of processes resulting from stimulation, including the oxidations, the contraction-changes and the other special features of the response.

That the action-current as well as the mechanical response of a muscle is suppressed by anesthetization has long been known. In nerve also anesthesia abolishes the action-current. Now, on the foregoing hypothesis, the electrical variation is the expression of some alteration in the plasma-membrane, involving a temporary increase of permeability. Höber has found that potassium salts, which deprive nerves of irritability and render them locally negative, cause at the same time a visible alteration in the axis-cylinders; these structures swell and stain more diffusely; he found further that these effects are checked or prevented if the nerves are first anesthetized with ethyl urethane. Experiments on voluntary muscle gave analogous results. If a frog's muscle is partly dipped into an isotonic solution of a potassium or rubidium salt the tissue contracts somewhat and becomes locally negative; this effect is also inhibited or retarded in the presence of an anesthetic.[6] If the local negativity is the expression of a change produced by the salt in the colloids of the plasma-membrane, rendering the latter more permeable than before, Höber's results indicate that the anesthetic decreases the susceptibility to such changes of permeability. If this is the case we can partly understand why the anesthetized tissue becomes less susceptible to stimulation, since stimulation involves an increase of permeability.

Quite recently at Woods Hole I have investigated the question of the nature of anesthetic action in a somewhat different manner, using an organism which seems unusually well adapted to throw clear light on this subject. If an anesthetic acts by so modifying the plasma-membrane of the irritable cell as to render difficult or impossible the rapid variations of permeability which are essential to stimulation, it ought to act similarly on other cells, *i. e.*, it should protect these cells also against the action of permeability-increasing substances or agencies. If an organism can be found whose cells undergo immediate and obvious increase of permeability under conditions which at the same time cause stimulation, it should become possible to determine whether suppressing the stimulating action of a given agency is equivalent to a suppression of its permeability-increasing action. The two effects ought to show a definite parallelism if the above hypothesis is well-based. The organism which I have used is the larva of the marine annelid *Arenicola cristata*. This organism shows

[6] *Cf.* Höber, *Pfluger's Archiv*, 1907, Vol. 120, p. 492.

anatomical features of the required kind. It is a small, worm-like trochophore about 0.3 mm. long, swimming by two ciliated rings and possessing a well-developed musculature of longitudinal fibers. The body cells are permeated with a yellow or brownish pigment, so that when the larvæ are collected in a dense mass (which can readily be done by taking advantage of their strong heliotropism) they appear dark brown in color. Now if such a mass of larvæ is brought suddenly into a pure isotonic NaCl solution, they instantly contract strongly and remain thus contracted for twenty or thirty seconds, after which they slowly relax. During the period of contraction the yellow pigment diffuses rapidly into the solution and colors the latter bright yellow; *i. e.*, strong stimulation of the muscle cells is associated with marked increase in the permeability of the pigment-containing cells. The cilia cease and undergo rapid disintegration at the same time. If now instead of using pure NaCl solution, we bring a similar mass of larvæ into NaCl solution to which a little calcium or magnesium chloride has been added, a strikingly different effect is seen. Stimulation is slight and transitory, there is no immediate loss of pigment, and ciliary action continues uninterrupted. The general toxic action of the NaCl is also greatly lessened. It can thus be shown that pure solutions of sodium salts cause strong stimulating and permeability-increasing effects, both of which are simultaneously prevented by the addition of a little calcium or other antitoxic salt. Prevention of permeability-increase runs parallel with prevention of stimulation. Magnesium salts in pure isotonic solution exhibit an action which is apparently the reverse of that shown by sodium salts. Larvæ brought into $m/3$ $MgCl_2$ show no stimulation, no loss of pigment or destruction of cilia, and little or no immediate injury. On the contrary all muscular movements cease in a few seconds and the larvæ remain permanently motionless during their stay in the solution (except for the cilia which remain active). The effect of the solution is reversible; on return after a few minutes to sea-water, the normal activities at once return. The magnesium salt shows typical anesthetic action, *i. e.*, it renders stimulation difficult or impossible. It also hinders increase of permeability. If larvæ that have lain in $m/3$ $MgCl_2$ for a few minutes are suddenly brought into $m/2$ NaCl, no immediate effect is seen—neither stimulation nor loss of pigment. The toxic action of the pure NaCl is also much less than when the transfer to this solution is made directly from sea-water. In other words, the $MgCl_2$ renders the plasma-membranes resistant to the permeability-increasing or cytolytic action of the NaCl solution; and at the same time it renders the irritable elements resistant to stimulation. The action of the $MgCl_2$ must depend on an alteration of the cell-surfaces, since this salt enters living cells with extreme slowness, if at all. We must conclude that in this instance at least the anesthetic action depends on a modification of the surface-layers or plasma-membranes of the irritable cells or elements.

I have found that lipoid-solvent anesthetics produce effects which are essentially identical with those of $MgCl_2$. The case of ethyl ether, the most widely used of all anesthetics, may serve as an illustration. In a .7 per cent. solution of ether in sea-water *Arenicola* larvæ immediately cease all muscular movements; the cilia show more resistance to anesthesia and remain active. If now the larvæ are transferred to $m/2$ NaCl solution containing the same proportion of ether—so as to preserve the state of anesthesia—no contraction or loss of pigment follows, the cilia continue their activ-

ity, and the injurious action of the pure NaCl is relatively slight. Bringing larvæ from normal sea water directly into ether-containing NaCl solution also causes little or no stimulation or loss of pigment, and the cilia and body cells are protected against the injurious action of the solution. Thus in the presence of the anesthetic the salt solution fails to show its normal stimulating and permeability-increasing action, and its toxic or cytolytic action is greatly diminished. Anti-stimulating and anti-cytolytic actions run parallel with each other.

I have studied the action of a large number of anesthetics in this manner. Those which promptly and completely anesthetize *Arenicola* larvæ in sea-water show, when dissolved in NaCl solution in the proper proportions, effects which are essentially identical with those just described, though varying in degree with the different anesthetics. Alcohols (methyl, ethyl, propyl, butyl, amyl, capryl), the urethanes (methyl, ethyl, phenyl), other esters like ethyl nitrate, acetate, propionate, and compounds like chloretone, acetanilide, paraldehyde, nitromethane, chloroform, acetonitrile, all decrease or prevent the stimulating and permeability-increasing action of pure NaCl solutions when present in the concentrations which cause typical anesthesia in sea-water. They also show well-marked protective or anti-cytolytic action. Other anesthetics, among which are chloral hydrate, benzol, phenyl urea, and chloralose, act more slowly than those just mentioned, and if larvæ are brought suddenly into their solutions in $m/2$ NaCl, stimulation and loss of pigment occur very much as in the pure salt solution. A parallelism between permeability-increasing action and stimulating action is thus seen throughout. If the one effect is decreased or prevented so also is the other.

The exact concentrations most favorable for anesthesia and prevention of permeability-increase are characteristic for each substance and have to be determined empirically. In a series of homologous compounds, like the alcohols or the fatty acid esters, the molecular anesthetic action increases rapidly with increase in molecular weight and in lipoid-water partition-coefficient. The same is true for the vertebrate central nervous system, as Overton and Meyer have shown. Overton's observations on tadpoles show a close parallelism with my own in these respects. The concentrations required to anesthetize *Arenicola* larvæ are, however, higher in every case—usually three to five times higher—than for tadpoles. Possibly the higher salt content of the tissue-media in marine animals is responsible for these differences; the order of relative action is the same in both organisms.

To sum up—it would thus seem that anesthetics produce their essential effects by modifying the properties of the semi-permeable plasma-membranes of the irritable tissues, making these structures more resistant to changes of permeability than normally. Since variations of permeability are essential to stimulation, the irritable tissue is thus rendered temporarily insensitive or irresponsive.

How does the anesthetic produce these effects? Osterhout has recently shown that anesthetics decrease the electrical conductivity of plant tissues, apparently by decreasing the permeability of the plasma-membranes to ions;[7] and it may be that in irritable animal tissues also the permeability normal to the membranes is similarly decreased during anesthesia. If the distinctive action of the anesthetics is to *decrease* permeability, its presence in the tissue will naturally oppose increase of per-

[7] Science, Vol. 37, 1913, p. 111.

meability and hence interfere with stimulation. The osmotic motor mechanisms of plants, whose action depends on sudden increase of permeability, may in fact readily be rendered irresponsive by anesthetics, as Claude Bernard pointed out long ago in his classical lectures on the life-phenomena common to animals and plants. Or the explanation may be somewhat different. The anesthetic may leave the resting permeability of the membrane the same as before—or perhaps may change it in either direction—but alter its properties so as to decrease the readiness with which the permeability is changed by other agencies acting on the membrane. Changes of condition, electrical or otherwise, that normally act as stimuli would then no longer affect the membrane, and would hence cease to stimulate. But whatever general interpretation we adopt, it is demonstrable that the properties of the membranes are altered during anesthesia in such a way as to make increase of permeability more difficult than in the normal sensitive state of the irritable tissue.

Is this the whole explanation of the anti-stimulating action of anesthetics? Nothing but further experimentation can answer such a question. Suppression of stimulation is however the essential effect to be explained. It must be remembered that any specific response to stimulation comprises a series of mutually interdependent processes, beginning with the one caused directly by the external agent, and ending with the special physiological activity, or response, characteristic of the tissue. It seems more likely that the anesthetic interferes with the *initial* process of such a series than with one occurring later—such as the increase in oxidation or other special effect. The evidence which I have cited indicates in fact that the primary process in stimulation is a *membrane-process,* and that it is this process which is modified by the anesthetic. This is why the succeeding and outwardly more evident effects of stimulation are also modified in the way that we observe.

It is well known that an influential group of physiologists, headed by Verworn, maintain that a suppression or prevention of oxidation-processes is the essential basis of anesthesia. Various facts are adduced in support of this theory. During anesthesia the oxidative metabolism of the tissue is diminished. This fact in itself is equivocal; stimulation causes increased oxidations in many tissues, and suppression of stimulation prevents this effect along with the others. Lack of oxygen arrests many physiological activities that are dependent on its presence, but this fact again does not justify Verworn's identification of narcosis and asphyxia. Other facts seem more consistent with this view. Fröhlich and Heaton find that the recovery of nerves from anesthesia is imperfect or delayed in absence of oxygen; Ishikawa, another pupil of Verworn's, finds the same for Amœbæ; from which they conclude that suppression of oxidations is the essential feature of the condition. These observations merely show once more that the cell or tissue requires oxygen in order to exhibit its normal properties. Mansfeld finds that the concentration of anesthetic required to anesthetize tadpoles is less when oxygen is deficient than when it is abundant; *i. e.,* anesthesia and asphyxia show additive relations to each other. This again is equivocal. The action of nerve-cells is intimately dependent on a good supply of oxygen; when oxygen is deficient their excitability is lowered, and along with this the degree of anesthesia required to abolish excitability. Other parallels of similar nature seem open to objections of the same kind. On the other hand, nerve trunks resist the lack of oxy-

gen or the presence of cyanide (which renders unavailable the oxygen present) remarkably well. Warburg finds that fertilized sea-urchin eggs anesthetized by phenyl urethane, so as to be incapable of cell-division, show nevertheless the same oxygen-consumption as the normal unanesthetized eggs. Again, lack of oxygen interferes only gradually with the ciliary action in many organisms, while anesthetics in sufficient concentration arrest the movement instantly. It seems necessary to conclude from these facts that the essential action of the anesthetic is of a more general kind, and consists in incapacitating some mechanism which is essential to the normal activities of the cell, whether these immediately require oxygen or not.

The evidence which I have reviewed indicates either that this mechanism is the plasma-membrane itself, or that it is closely dependent on the condition of the plasma-membrane. Any condition that renders the membrane incapable of responding to changes of condition by rapid changes of permeability and of electrical polarization has an anesthetic influence. This modification in the properties of the membrane may be produced either by changing the general condition of the colloids forming it—as in the case of magnesium salts or electrolytes in general—or by specifically altering the state of the lipoid-components, as by organic anesthetics. It is impossible to say at present precisely why the solution of an anesthetic in the lipoids of the membrane should thus alter the properties of this structure. The nearest physico-chemical analogy seems to be the so-called "protective action" of colloids, as exemplified in those cases in which the presence of one colloid interferes with or prevents changes of aggregation-state in another, *e. g.*, when gelatine prevents the precipitation of colloidal gold or platinum by a neutral salt like sodium chloride. Apparently the lipoids are related to the other colloids of the membrane in such a manner that the condition of the lipoids affects the entire properties of the colloidal structure, and so determines the effect which an electrolyte like NaCl, or a stimulating condition like an electric shock or mechanical impact, may have upon it. Hence when a lipoid-solvent acts upon the membrane, and dissolves in the lipoids of the latter, it may profoundly change the physical properties of the membrane and hence the responsiveness of the whole tissue or organism to stimulation. On this view the membrane is a main controlling factor in cell-processes, and by changing its state we may alter the entire physiological activity of the cell.

RALPH S. LILLIE
UNIVERSITY OF PENNSYLVANIA

PSYCHOLOGISTS AS ADMINISTRATORS[1]

CASUAL statements have frequently been made to the effect that many psychologists leave their professional careers to become administrators of one sort or another, or carry on executive work of a definite kind in addition to their activities as psychologists, with the appended implication that psychology, as a science, suffers a proportionately greater loss of effective workers on this account than do the other sciences. As illustrations of this loss, not a few well-known examples are cited. At first blush, the generalization thus made might be classed under the fallacy of *post hoc, ergo propter hoc,* but in order to escape this charge ourselves, we must submit the matter to some statistical presentation.

The executive positions to which academic men are obviously called are presidencies of colleges and universities, and deanships of departments within colleges and universities. Farther down the scale, viz., directorships of laboratories and headships of divisions and

[1] Read before the meeting of the Experimental Psychologists at Wesleyan University on April 12, 1913.